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(54) Title: KIT FOR SCREENING COMPOUNDS WITH LOW WATER SOLUBILITY

(57) Abstract: The present invention is concerned with a multipurpose kit and methods thereof for obtaining in vitro as well as in vivo data. It describes a kit comprising preferably more than one container or such like comprising homogeneous solutions, dispersions or suspensions of at least one Common component. The Common component has the potential and capacity to solubilise or form complexes with new as well as existing compounds with low water solubility, for the assessment of physicochemical and/or biological properties in models. The physicochemical data may be e.g. solubility and membrane lipid interaction potential, whislt the biological data may include but not limited to information on membrane permeability, bioavailability, efficacy, toxicity, pharmacokinetic (PK), distribution, elimination profiles, local tolerability, etc. The kit allows for an integrative approach, whereby the data from a series of tests can be collated and extrapolated more appropriately and reliably. The kit and methods thereof screens materials for pharmacokinetic and other biological properties for intravenous, intramuscular, subcutaneous, oral, topical, or any other route of administration to a living organism.

Kit for screening compounds with low water solubility

FIELD OF THE INVENTION

This invention relates to a multifunctional kit and methods thereof for screening materials for desired information. The invention comprises preferred components to solubilise compounds with low water solubility to obtain information on physicochemical properties. It is also a multipurpose vehicle or tool for assessment of biological properties in vitro and in vivo.

BACKGROUND OF THE INVENTION

It is well known that by the very nature of drug discovery methods, at least 30% to 40% of compounds with potential activity emerging from molecular modelling, combinatorial chemistry and high throughput screening methods are lipophilic and have poor aqueous solubility. It is generally preferred that compounds are presented in a molecular state or at least in the finest possible colloidal dispersion to enable maximum interaction with receptor surfaces. Organic solvents such as DMSO (dimethylsulphoxide), DMF (dimethylformamide) and NMP (N-methylpyrrolidone) are frequently used as 'universal solvent' to dissolve both lipophilic and amphiphilic compounds in High Throughput Screening (HTS).

In the early research stage to characterise a compound further using in vitro cell cultures, the somewhat limited knowledge on the solubility characteristics and restricted availability of 'safe' solvents and vehicles often pose problems. Should the research scientist choose to use (DMSO) as a solvent, then likely precipitation during serial dilution could give false results which may underestimate the efficacy or toxicity of the compound. Alternative solvents and detergents other than DMSO are just as likely to be detrimental to cell cultures. If the test material is tested orally in animal or human trials in a solvent, the dissolved drug may precipitate as large crystalline or amorphous particles which may be insoluble in the gastrointestinal tract. Likewise, after parenteral administration the drug may precipitate at the injection site or in the circulation and cause local and systemic side effects. In either case the bioavailability will be low because the insoluble material may

not be able to interact with receptor surfaces. Therefore wherever possible, pre-clinical in vitro and in vivo studies should be carried out using methods that allow optimal interaction between test and host materials by presenting the test material in a stable molecular state for the duration of the test. The method for effecting molecular dispersion should be viable and cost effective whilst the compositions must be safe and functional. Furthermore the lipophilic compound must remain in a mono molecular state across the entire dilution and dosing range to be tested. Preferably, the solubilisation principle utilised should be the same for all the tests, and the components(s) used therein should not be harmful, be suitable for most administration routes and for further development and eventual product registration. The present invention meets the aforementioned requirements for a desirable test composition. By employing a multipurpose and multifunctional kit, the results obtained from the various tests may be compared and extrapolated more reliably. As a result development timelines and costs to develop problem drugs with low water solubility can be considerably reduced.

SUMMARY OF THE INVENTION

The present invention is in the area of "Solubilising compositions" and "Integrative kits". In one aspect, the invention is concerned with compositions which enable efficient and high solubilisation capacity for compounds with low water solubility. Thus it provides a medium for screening lipophilic compounds for physicochemical properties to establish parameters for solubility and membrane lipid interactions. In another aspect, the invention provides a kit to obtain biological data from in vitro and in vivo assays. In a preferred embodiment, the kit comprises one or more Common compositions in one or more suitable containers or the like for use in situ, and for transport and long term storage and later use. More than one such container may be present in the kit which includes instructions and guidelines to prepare a composition with a lipophilic compound. The resulting test composition can be diluted with an aqueous physiological buffer or other aqueous media. The compound is maintained in molecular dispersion during and after dilution without precipitation of crystals or large particles. The kit is generally suitable to screen materials for comprehensive physicochemical as well as biological data. The analyses are carried out using either in vitro or in vivo tests. By using membrane lipids to form molecular associates, the kit is suitable for most routes of administration to animals and humans and is

not detrimental to cell cultures. Membrane lipids, e.g. phospholipids, are generally recognised as safe (GRAS) and may be used freely in pharmaceuticals, food, and cosmetics and other purposes. The invention provides for a means of identifying a compound that may be applied to pharmaceuticals, veterinary medicine and husbandry, agriculture, horticulture, aquaculture, fermentation and vaccine production, and other areas where one or more desired property of the compound can be evaluated and identified to enable selection of lead candidates and compositions. It further allows the feedback data to be incorporated and extrapolated into a finished product.

Traditional screening methods do not allow for an integrative approach, whereby the data from a series of tests on different models and substrates may be collated and extrapolated more appropriately. Furthermore, the prior art does not disclose a multipurpose kit and methods thereof, comprising Common components to solubilise, or form molecular associates for analysing compounds for desired information comprehensively.

In one aspect, the invention provides a tool kit comprising up to several Common compositions in which the solubility of a test compound may be tested with the view to screening for a stable mono-molecular solution, or dispersion. The kit contains preferably membrane lipids in solution or dispersion in a hydrophilic medium in various concentrations. Surprisingly, compared to the use of the hydrophilic medium without membrane lipid component, the kit allows significantly increased solubility. Solubility may be increased in some cases by as much as 100 times given the proper identification of associate forming component and compositions thereof. This may be indicated by strong interaction with membrane lipids and possibly increased membrane permeation. Unexpectedly, when a test compound is dissolved in the kit, it can be infinitely diluted with an aqueous medium without precipitation of insoluble crystalline or large amorphous particles. Therefore a wide concentration range of the test compound in molecular dispersion may be obtained and used for obtaining biological data in cell models, cell lines, components of living organisms, micro organisms and living organisms, etc. The kit also provides for a particularly suitable, non toxic vehicle to screen for pharmacokinetic properties such as bioavailability as well as to carry out toxicity studies on compounds in animals and humans.

In another aspect, the invention identifies the best combination of essential components and the composition for solubilising, or preparing molecular associates with test materials and which may be used in formulations. The kit provides an ideal means for screening purposes. It bridges the requirements between in vitro, in vivo and tests on living organisms by employing Common components in a vehicle to carry out the various tests whilst maintaining the compound in a mono molecular state. It avoids the need to develop separate and different vehicles to carry out the numerous tests, thereby accelerating development timelines and reducing costs. These advantages have not been demonstrated in prior art methods used for screening compounds.

The kit comprises Common compositions and components for use therein according to the intended route of administration. For oral and topical administration, compositions preferably comprising diacyl and monoacyl lipids on their own, or in any combination may be used diluted or undiluted with an aqueous medium,. For intravenous testing, the compositions may comprise an isotonic diacyl membrane lipid dispersion optionally with minor amounts of a monoacyl component. The compound can be added to a liquid test composition either as a solid or in solution. A kit may comprise at least one suitable container or the like holding a pre-measured amount of a composition comprising a Common component. Preferably, the kit comprises more than one such container each holding the same or different concentrations of a Common component. The kit can be used as a multipurpose vehicle for,

i) obtaining information on key physicochemical data such as solubility, partition coefficients, etc;

ii) obtaining information on transfer properties between membrane interfaces, or across/over a series of membrane bilayers using cell models, cell lines and bio-assays, etc;

iii) identification of lead drug candidates, components, combinations and compositions using homogeneous solutions or molecular associates for desired absorption, bioavailability, other pharmacokinetic properties and efficacy;

iv) administration to living organisms.

PRIOR ART

In the prior art the following methods and components have been employed to solubilise amphiphilic and lipophilic materials in place of more harmful organic solvents such as dimethyl sulphoxide, dimethyl formamide and N-methylpyrrolidone. Because of various reasons which may be intrinsic local and systemic toxicity, lack of solubility of the compound in the vehicle and risk of precipitation, inconvenience, high costs and unpredictability of the method to solubilise or complex materials, the methods are mostly unsuitable as test vehicles or means for screening materials comprehensively for biological properties in vitro and in vivo.

Prior art methods relating to solubilisation and specific methods for screening compounds for desired characteristics include the following:

WO 99/08112 describes methods of identifying biological agent compositions involving segmented copolymers. The method disclosed may be used to test a biological agent for biological properties using a cell, animal, plant or other biological model, or for measurement of a chemical or physical property in a test tube, or a theoretical model. The method is essentially confined to the specific use of said polymers and methods for preparing the polymers. It does not disclose a multipurpose test kit using Common components to solubilise lipophilic compounds in situ and for screening purposes.

US-A-5,707,873 discloses a method of assessing mixed lipid transport properties of a drug. The method provides a mixed lipid composition which incorporates a drug in colloidal particles, applying the particles to a size exclusion chromatography column, eluting free drug and drug incorporated into mixed lipid particles from the column, and determining the elution profiles of the free drug and the drug incorporated into mixed lipid particles. Drugs which elute with the mixed lipid particles are considered to have stable transport properties. This known method of the prior art cannot be used as a vehicle, particularly in living organisms to obtain biological data.

Phase I trial of liposomal muramyl tripeptide phosphatidyl ethanolamine in cancer patients has been reported in J. Clin. Oncol. 1989,7: 1915-25 using a dry membrane lipid ly-

ophilisate to which a Tc99m pertechnetate aqueous solution was added. The liposomal suspension formed was administered intravenously to cancer patients to study the body distribution of the liposomes prepared from the special lipid. The disclosure does not teach the use of a liquid membrane lipid compositions as a kit for routine screening purposes.

EP-B-0 158 441 relates to pro-liposome compositions based on membrane lipids, to a method of making large volumes of lipid vesicles by the addition of aqueous fluid to these compositions, and to aqueous dispersions of vesicles. The compositions contain water soluble, or oil-soluble biologically active compounds. They may also contain an organic solvent suitable for injection purposes, such as ethanol. It does not teach the in situ preparation and use of membrane lipid compositions in an integrative kit for routine screening purposes of biological substances with low water solubility or as a Common component making up a screening kit.

Immunodiagnostic methods for macromolecules and other hydrophilic compounds using membrane lipids are further disclosed in US 4,738,932; US5,776,487; and US 5,968,549. US 5,800,833 discloses the therapeutic use of a kit comprising preformed liposomes having a methylamine concentration gradient across the lipid bilayer, and an active compound.

DETAILED DESCRIPTION OF THE INVENTION

Definitions:

"Common " in this specification refers to similar, or preferably the same type of features.

"Common components" and "Common compositions" may be characterised by, i) the potential and capacity to either solubilise or dissolve compounds by means of forming complexes, associates and aggregate structures whereby the molecules are in co-dispersion, preferably ii) use in at least one of the following categories: pharmaceuticals, food and cosmetic products.

"Kit" covers compositions comprising pre-measured amounts of Common components which are excipients for solubilising or forming associates, and methods thereof to screen

and analyse test materials and components mutually for desired information. A kit comprises at least one Common composition and its container or more usually a plurality of containers and contents, for single use or multiple use. The container may be test tubes, sealed unit(s) such as vials and the like with closures, for holding, storing, transporting and commercialising the pre-measured compositions and components used therein. Kit further includes any packaging, labelling, inserts, method and instructions for use. A kit may be used in combination with any apparatus for carrying out the tests. The analysis or analyses may be carried out on models and substrates such as cell models, cell lines, components of living organisms, living organisms, using any method. The data obtained includes but is not limited to physicochemical and biological properties as defined hereunder.

"Physicochemical property", "physicochemical characteristic" or "physicochemical feature" includes but is not limited to data on solubility, lipophilicity, rate and extent of solution, partition coefficients, membrane interactions, membrane affinity, membrane lipid solubility, transfer potential between membrane structures, receptor binding and release, molecular and dispersion state, UV, IR, near IR and Raman spectra, mass spectra, X-ray diffraction patterns, surface plasma resonance, complex formation, crystal forms, polymorphic and amorphous forms, particle size, stability, etc. It includes any physical characteristic or chemical property which characterises the physical state and/or chemical composition of a compound. The determinations may be carried out using either cell models or test tubes, or other instruments or apparatus, including computational equipment.

"Biological property", "biological characteristic" or "biological feature" includes but is not limited to data on absorption from gastro intestinal tract, systemic circulation, mucosal and membrane surfaces. It encompasses pharmacodynamic and pharmacokinetic properties such as bioavailability, excretion, elimination, toxicity, tolerability, binding to blood components such as serum proteins, membrane affinity, transfer potential between and within membranes, receptor binding and release. It includes any characteristic that relates to biological, physiological, clinical and pathological states. The determinations may be carried out either in vitro using models, in cell lines, Caco-2 cells, animal perfusion, tissue perfusion, or other components of living organisms, or in vivo in living organisms which include animals and humans.

"Activity" describes the antagonism, agonism, inhibition, neutralisation, and other physiological, pharmacological and biological effect elicited on the target or host.

"Material" includes any chemical or biological substance, any organic or inorganic element or compound, including nucleotide, single nucleotide, single nucleotide polymorphism and precursors thereof, or nucleotide sequence (including DNA and RNA sequences, gene, vector or construct including plasmids, or viruses), host organism (including yeast, fungi, algae, protozoa and hybridomas, eukaryotic or prokaryotic cell line or expression system or any development strain or product of that cell line or expression system), protein (including any peptide or amino acid sequence, enzyme, antibodies or protein conferring targeting properties and any fragment of a protein or a peptide enzyme or anti-body), cell cultures, vaccines, drug or pro-drug, assay or reagent, fermentation media, or any genetic or biologic material, or membrane lipid component, or micro-organism or multi-cellular plants or components of living organisms. They may belong to product groups like pharmaceuticals, nutraceuticals, biopharmaceuticals, biotechnology products, food components, cosmeceuticals, veterinary and in vitro and in vivo diagnostic products. The expressions 'material', 'compound' and 'drug' are used interchangeably in this specification to illustrate the particular application more appropriately.

"Test material" refers to a hydrophilic, lipophilic or amphipathic active material or compound with low water solubility which either dissolves, or forms molecular associates or complexes with component(s) in the kit for the analyses of physicochemical and biological data.

"Component(s)" refers to a constituent(s) in a test composition or formulation but excludes the test material.

"Bioavailability" defines the extent and rate that a drug or other substance is either absorbed or taken up by a specific tissue or organ after administration, or interacts with a target cell and/or a receptor.

"Molecular associates", "associates", are complexes formed between a compound with low water solubility and the Common component(s) in a kit by means of solubilisation, molecular co-dispersion, or mono-molecular solution, without changes to the chemical architecture. The associates include but are not limited to micelles, inverted or reverse

micelles, mixed micelles, vesicles, micro-emulsion oil droplets, complex emulsion droplets. The definition also extends to colloidal amorphous co-precipitates, adducts, clathrates and inclusion compounds.

" Compound with low water solubility" includes lipophilic, hydrophobic, amphiphilic or amphipathic compounds that require more than 10 parts of water to dissolve 1 part of the compound. It spans the definitions between sparingly soluble (from 10 to 30) to insoluble compounds (10'000 and over) and includes particularly the very slightly soluble (from 1000 to 10,000) to insoluble (10,000 and over) as defined in USP 24.

"Molecular association" and "mono molecular solution" is achieved if not more than 10% of un-associated test material is retained on a 450 nm polycarbonate membrane filter after filtration of at least 1:5 dilution of the kit composition containing the associated test material with distilled water. The definition also includes a clear solution of the solubilised compound.

The current invention allows a test material which may be a discovery or existing compound to be tested in a kit for physicochemical properties, or it may be used for screening a compound on a host or model which may be a component of living organisms or a living organism, with or without further dilution, to obtain relevant biological data. Preferably, one of the components is a membrane lipid, most preferably a phospholipid. In a less preferred version cyclodextrin may be used. Uniquely, the invention allows for the comprehensive screening of the properties of materials in a solubilised state as molecular associates. The screens may be any type of physical and biological test carried out in vitro and in vivo, on living organisms and across numerous administration routes e.g., intravenous, subcutaneous, intramuscular, oral, topical and inhalation. Data may be obtained to assess transfer between membrane interfaces, or across a series of membrane bilayers using all types of lipid membranes and structures, including information on possible penetration of the blood-brain membrane barrier using appropriate targets. From a series of test materials one or more candidates with the desired membrane interactions and transfer potential may be selected. The two properties may be predictive of good bioavailability or uptake by the target or host. Furthermore, for a particular drug candidate the most

appropriate components, dosage form and route of administration may be identified and evaluated by means of the invention.

Accordingly, the present invention involves a liquid or dispersion typically comprising at least one of the following examples in a kit which may be test tube(s) or other suitable container(s),

i) 0.1 -90% of a membrane lipid, dissolved, or homogeneously dispersed in a hydrophilic medium, and optionally containing other excipients;

other Common components that may be used are:

ii) 0.1% - 90% of a cyclodextrin in place of membrane lipids or, combinations of membrane lipids and cyclodextrin;

iii) 0.1 – 20 % of a pharmaceutically acceptable surfactant dissolved, or homogeneously dispersed in a hydrophilic medium and optionally containing other excipients;

iv) a micro emulsion comprising 0.1 to 50% of water and a water miscible organic solvent and 0.1% to 50% of a mixture containing a lipophilic medium and at least one surfactant;

v) 0.1 – 20 % of a mixed micellar composition containing a bile salt and a membrane lipid dispersed in hydrophilic medium, and optionally containing other excipients;

vi) 0.1 to 20% urea dissolved in a hydrophilic medium;

Another embodiment of the kit comprises:

vii) at least 0.1 %, preferably between 1% to 70% of at least one membrane lipid, or cyclodextrin on its own, or combinations of membrane lipid and cyclodextrin dispersed or dissolved in at least one hydrophilic medium, and optionally containing other excipients;

In a preferred embodiment the test kit comprises:

viii) at least 0.1 %, preferably between 0.10 % to 70% of at least one membrane lipid, dispersed or dissolved in at least one hydrophilic medium, and optionally containing other Common components and excipients.

All the percentages above are parts by weight. For the avoidance of doubt, "hydrophilic medium" includes one of the following three liquids, i) water or aqueous medium, ii) at least one water miscible organic solvent, iii) mixtures of water or aqueous medium with at

least one water miscible organic solvent. Preferably, the organic solvents are permitted for pharmaceutical, food and cosmetic uses.

The kit comprises Common components that have the potential and capacity for solubilising, or forming molecular associates with a wide range of test materials using a variety of dilution protocols. In many respects, the chemical architecture of the component is not a limiting factor, as long as it is not harmful and may be used with little or no regulatory and safety restrictions. The invention is particularly suitable to screen materials by employing about 10 mg or more of test substance in total for each screening application. The invention is not limited to screening lipophilic compounds, it may also be used as a vehicle to assess the activity and bioavailability of water soluble compounds having lipophilic regions (e.g. high MW proteins with lipophilic domains). Surprisingly the invention is also suitable for screening hydrophilic compounds with low absorption and bioavailability. This may be due to the fact that kits comprising e.g. phospholipids and some surfactants, may block the action of P-glycoproteins pumps present in cell membranes. Therefore the invention helps overcome the difficulties when evaluating materials with low uptake which may be due to the action of efflux pumps. It rationalises the selection of lead compounds and thereby improves their delivery by using a screening method that recognises the problem.

The invention provides an integrative kit which is suitable for solubilising compounds with low water solubility and analysing for physicochemical and biological properties in vitro and in vivo. It provides a multipurpose and multifunctional kit which involves preparing one or more compositions comprising homogeneous solutions, dispersions or suspensions of, i) at least one Common component which has the potential and capacity to dissolve, or form molecular associates, ii) water or a water miscible organic solvent, iii) mixtures thereof, iv) optionally further excipients, and one or more of the following steps,

a) forming a solution, or molecular associates by mixing said compositions with a test material with low water solubility and, optionally after dilution with water, analysing the physicochemical properties,

b) forming a solution, or molecular associates by mixing with a test material with low water solubility and, optionally after dilution with an aqueous medium, adding said

composition to cell models, cell lines or components of living organism and analysing the physicochemical properties,

c) forming a solution, or molecular associates by mixing with a test material with low water solubility and, optionally after dilution with an aqueous medium, administering said composition to living organisms and analysing the biological properties.

The kit may further comprise one or more containers, units or vials holding in each unit a pre measured amount of a homogeneous solution, dispersion or suspension of at least one Common component for single or multiple use. The kit may be prepared and used in situ, or it may be end packed into suitable containers from a bulk solution or suspension, for transport and long term storage, for use at any time.

In one aspect, the invention provides for a medium for testing solubility and other physicochemical properties of materials without the requirement to attach ligands, haptens, antibodies, antigens or analytes to the solubilising component(s). In another aspect, the invention involves a Common vehicle to carry out mutual testing of materials and components by assessing biological properties on a model or in a living organism. It must be clearly understood that the compositions and methods involved in the current invention are not employed for therapeutic purposes i.e. treatment, but essentially for screening and selection of a material and components for desired properties with the object of using the feedback data to develop an optimum formulation.

The present invention may contain water miscible organic solvents which are approved for use by regulatory authorities in human and veterinary products, i.e. ethanol, glycerol, propylene glycol, PEG 300 and PEG 400. In certain situations, it is possible that the vehicle may contain predominantly water or an aqueous medium, as much as 99.9% by weight. Where the compound to be tested is extremely insoluble, water miscible organic solvents such as DMSO, DMF, NMP may be used with a Common component to dissolve, or solubilise the compounds. Usually, minimal quantities should be used, e.g. less than about 20%, preferably about 10% by weight with the proviso that the amount used does not have any adverse effect on the host and does not interfere with the screening process.

Method

The kit may involve individual containers for either single use or multiple use. The compositions may be prepared in situ for immediate use or they may be prepared in large volumes and measured amounts are filled into individual units for storage and transport. For assessing solubility profiles, a test compound may be added to the pre measured compositions in the kit. The complex or molecular associates formed prior to formation of a turbid suspension may be evaluated for membrane interactions in cell models, cell lines, etc. For in vivo studies, all that is required is to dissolve or complex a measured amount of test material to a kit and evaluate the resulting composition in living organisms.

The present invention not only simplifies screening but it also helps to select lead compounds, components and compositions more efficiently. When naturally occurring membrane lipids are included as Common components in the kit the screening programs allow better correlation, integration and possible extrapolation of membrane interaction data between pre-clinical, in vitro and in vivo studies. As a result compounds with more favourable intrinsic membrane interaction may be recognised in the first instance. Secondly, for compounds that have poor intrinsic membrane affinity, the most appropriate remedy e.g. the most effective components for presenting the compound in a membrane 'friendly' and absorbable state may be identified. In most cases this will not be the formulation for marketing. However a marketable formulation may be selected for development more easily because of the information gleaned. A major benefit of the invention concerns the use of acceptable and Common components and excipients for screening purposes where the component(s) used for forming molecular associates for solubilising is a membrane lipid, cyclodextrin, combinations of membrane lipid and cyclodextrins, or other Common components which may require minimal or no further toxicity work. This facility and seamless transfer of technology and components used therein from initial screening to the development of a final dosage form for administration to a living organism is possible because of the use of a Common kit for all the tests. The invention has not been exploited previously for screening purposes. It offers considerable savings in development time and costs because fewer changes will be required to bridge the different requirements between the tests. Thus the invention enables mutual identification and selection of lead com-

pounds and components and the most appropriate compositions in the fastest possible time.

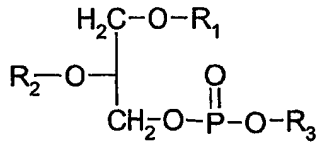
The lead candidate selected using the kit may be formulated into liquid, gel-like or solid dosage forms, preferably using the Common components employed in the kit. Membrane lipid components used in compositions for delivering biologically active compounds for therapeutic use in living organisms is an example of a component that is preferred. These are extensively described in US-A-5,004,611, US-A-5,053,217, EP-B-0 158 441, US-A-5,141,674, EP-B-0 309 464, EP-B-0 759 736, and EP-B-0 724 430. It should be understood that the invention may also cover a formulation containing a compound that has been screened and selected using the information provided by the kit disclosed in this specification, with the proviso that said formulation includes at least one of the solubilising or associate forming components used in the kit.

Alternative complexing or associate-forming components to preferred membrane lipids are alpha, beta or gamma cyclodextrins where oral administration is envisaged and preferably hydroxypropyl-beta and sulphobutylether-beta cyclodextrin when parenteral administration is intended. The amounts used may vary between 0.1- 90% by weight dissolved in water or aqueous medium. Other components that are suitable are polysorbate 20 or 80 (Tween 20® and 80®), polyoxyl castor oils (Cremophor EL® and RH®) dissolved in water at a concentration of 0.1 -20% by weight. Preferred associate forming mixed micelle compositions comprise a bile salt, preferably sodium glycocholate, mixed with a lecithin at preferably 1:1 molar ratio up to 100 mg total lipid and cholate mixture per ml. Particularly preferred components are membrane lipids which may be a phospholipid, or mixtures of phospholipids and cyclodextrins, in any ratio up to 1:1. The phospholipid may contain either only diacyl (PC) or monoacyl phospholipid on its own, or a mixture of diacyl (PC) and monoacyl (MAPC) components in a ratio of 1:20 to 20:1, preferably 1:10 to 10:1, most preferably 1:5 to 5:1, parts by weight. Preferred diacyl phosphatidylcholines are soy PC, Egg PC, POPC (1-palmitoyl, 2-oleoylphosphatidylcholine), OOPC (1,2 dioleoylphsophatidylcholine) and partially hydrogenated Soy and Egg PC with a similar fatty acid composition as POPC. Preferred monoacyl counterpart is enzyme modified (Phospholipase A2) soy PC, followed by Egg PC, 1 -palmitoyl PC, 1 oleoyl PC, 1-stearoyl PC. Solvent type solubilising components which may be employed on their own without

associate forming components, although this is not preferred are, ethanol, polyethylene glycol 300 and 400, propylene glycol, glycerol, ethyl lactate mixed with water up to maximum of 50 % w/w. The above list is not an exhaustive list of Common components (as defined) that may be used in the kit. Other suitable components such as e.g. urea which have associate forming properties i.e. clathrate or adduct formation and with little or no restrictions for use in pharmaceuticals, food and cosmetic products may be included in a kit to screen topical applications, to illustrate the versatility and key features of this invention.

The kit comprises preferably:

i) at least one membrane lipid, preferably at least one phospholipid with the formula,



(I),

R_1 represents C_{10}-C_{20}acyl;

R_2 represents hydrogen or C_{10}-C_{20}acyl;

R_3 represents hydrogen, 2-trimethylamino-1-ethyl, 2-amino-1-ethyl, C_1-C_4alkyl, C_1-C_5alkyl substituted by carboxy, C_2-C_5alkyl substituted by carboxy and hydroxy, C_2-C_5alkyl substituted by carboxy and amino, an inositol group or a glyceryl group or a salt of such compound;

ii) water and/or at least one water miscible, preferably pharmaceutically acceptable organic solvent; optionally,

iii) excipients and preservatives suitable for oral, parenteral, and topical administration purposes.

Other examples of membrane lipids are cardiolipin, sphingomyelin, cerebrosides, glycolipids and ceramids. These membrane lipids may be derived from absorption relevant biomembranes and bariers like brush border membranes, asterocytes, skin cells, epithelial

cells etc. natural plant or animal or microbiological sources, synthesised or partially synthesised and hydrogenated, including polyethylene glycol (PEG) derived diacyl and monoacyl equivalents.

Examples of water miscible, pharmaceutically acceptable solvents that may be used in the kit, depending on the particular circumstance or screening application, are e.g: ethanol, 96% ethanol, absolute glycerol, propylene glycol, ethyl lactate, polyethylene glycol 300, polyethylene glycol 400, 1,3 butandiol, succinic acid diethyl ester, triethyl citrate, dibutyl sebacate, dimethyl acetamide, dimethyl sulphoxide, glycerineformal, glycofurol (tetraglycol), isopropanol, lactic acid butyl ester, N-methylpyrrolidone, solketol, propylene carbonate, propylene glycol diacetate, tetrahydrofurfuryl alcohol, diethylene glycol mono ethyl ether, triacetin. The amount of solvent used is within the range of 1% to 99.9% w/w, preferably 20% to 99% w/w.

Examples of pharmaceutically acceptable liquid suitable for inclusion in a kit comprising associates which are micro emulsion droplets are, water for injection (e.g according to the United States Pharmacopoeia), benzyl alcohol, benzyl benzoate, triglycerides, medium chain triglycerides like Miglyol 810™, Miglyol 812™, Miglyol 812 N™, Miglyol 829™, Miglyol 840™, Miglyol 8810™, isopropyl myristate, isopropyl palmitate, ethyl oleate, (2-octyl dodecanol), laurin acid, hexyl ester, oleic acid, ricinus oil, sesame oil, soybean oil. These may be present at up to 50% by weight, preferably 1% to 30%.

Other preservatives suitable for use in kit compositions are anti-oxidants like alpha tocopherol acetate, ascorbyl palmitate and anti-microbial preservatives like methyl paraben and butyl paraben.

A kit is prepared as follows:

Solutions or homogeneous dispersions comprising solubilising or associate forming component(s) and optionally other pharmaceutically acceptable excipients are prepared and filled into glass vials and closed with a rubber stopper and an aluminium cap, or into another container suitable for single or multiple use. For parenteral screens the composition is sterile filtered though a 0.45 μm pore size membrane filter and filled in glass vials closed with a teflonised rubber stopper.

The following examples illustrate the invention. For illustrative purposes the test materials screened in the examples are typical lipophilic compounds with low water solubility. The examples are intended for illustrative purposes only and do not limit the scope of the invention.

Example 1

This example illustrates the screening of a test material for suitability in forming molecular associates with kits containing varying membrane lipid compositions.

10 mg of triamcinolone acetonide is added to a vial containing a kit with 250 mg lipid in 250 mg ethanol. The content of the sealed vial is left to dissolve for 1 hour at 50°C. The lipid-drug solution is added to 25 ml water and shaken for 5 minutes to form lipid associates. Approximately 5 ml of the bulk sample is filtered through a 200 nm pore size filter to determine the degree of association of the drug substance with the lipid. The amount of drug associated with the lipid is determined by HPLC.

Lipid composition of the kit w/w	Visual appearance of sample before filtration	Appearance of filter	Association (%)
95 % PC 1.0 % MAPC	Opaque	Some precipitate visible	75.7
28 % PC 62 % MAPC	Clear liquid	No precipitate on filter	95.5
12 % PC 80 % MAPC	Clear liquid	No precipitate on filter	91.9
Control	Cloudy with fine precipitate	Large amount of white precipitate visible	4.6

The results indicate that the association of the test material with the kit significantly increase the amount of drug passing through the 200 nm filter. The amount of test material passing through the filter increases from 4.6% (without kit) to over 95% when a kit com-

prising 28% PC and 62% MAPC is employed. The association of the test material with the kit containing 62% MAPC is higher compared to the kits containing either 1 % or 82% MAPC.

Examination of the solid associates may also be carried out after removal of the ethanol from a clear solution. The membrane interaction may be reflected by the association between the lipid components and test materials in the dry state. This may be obtained by analytical filtration after dispersing the solid in water.

Example 2

A similar screen as in Example 1 is performed using clotrimazole as the drug substance and ethoxy diglycol instead of ethanol. The results are presented in the table below:

Lipid Composition w/w	Visual appearance of sample before filtration	Association (%)
95 % PC 1.0 % MAPC	Opaque	79.5
Control	Opaque	21.2

Similarly the employment of the kit increases the association of the clotrimazole. In this case, there is a three fold increase.

Example 3

This example demonstrates the improved association due to kits having different membrane lipid mixtures in the kit.

10 mg each of miconazole is added to a first kit in a vial comprising 100 mg soya lipid (28% PC and 62% MAPC w/w) dissolved in 100 mg ethanol and to a second kit containing a higher proportion of MAPC (12%w/w PC and 80% w/w PC). The miconazole is left to dissolve in the kits for 1 hour. The contents of the vials are then removed and added to

25 g of distilled water and shaken for 5 minutes. Approximately 5 ml of the bulk sample is filtered through a 200 nm pore size filter to determine the degree of association of the drug substance with each kit. The amount of drug in the sample after filtration is determined by HPLC. The results are provided in the Table below:

Lipid Composition w/w	Appearance of sample prior to filtration	Appearance of filter	Association (%)
12 % PC 80 % MAPC	Clear liquid	No precipitate visible	93.9
28 % PC 62 % MAPC	Slightly turbid liquid	Some precipitate visible	70.3
Control (No lipid)	Dense Precipitate	A lot of precipitate visible	0.0

The association properties due to membrane lipid interactions are clearly demonstrated in this screen. Without the kit no drug is detected after filtering the solution through a 200 nm filter. In combination with the kit, more than 93% of the miconazole passes through the filter (the lipid composition of the kit was 12.2% PC and 80.5 % MAPC). If the lipid composition of the kit is 28.0% PC and 61.6 % MAPC, the degree of association is found to be only 70.3%.

The examples illustrate typically the use of a kit to evaluate physicochemical properties such as solubility and membrane interaction potential and capacity with test materials. The test material may be either an existing or a discovery compound. It is likely that test materials which have the greatest capacity to form molecular associates may also have improved biological properties when administered to a living organism. Therefore a composition with the maximum potential to form molecular associates may be identified and used for in vivo studies and to test further for biological properties in appropriate models.

Example 4

This example illustrates an example of an in vitro screen on a model which is cell lines using a kit according to the invention.

A stock solution of 20.22 mg of a water soluble lipophilic peptidometic (with a MW of 395) is added to 200 mg of a kit containing 100 mg of a lipid and 100 mg ethanol. This is made up to 10 ml with distilled water. 0.5 ml of the solution is applied to CaCo2 cell lines. 0.2 ml of the sample is collected every 30 min from the basolateral side of the cells and the amount of peptidomimetic is determined.

As a control, 20.16 mg of drug is dissolved in 10 ml of water. 0.5 ml of the solution is applied to another set of CaCo2 cell lines. 0.2ml of the sample is collected every 30 minutes from the basolateral side of the cells and the amount of peptidomimetic is determined. The results are provided in the Table below:

Time point (minutes)	Transport of active across cell (%)	
	Active alone	Kit and Active
30	7.3	7.3
60	10.9	18.1
90	15.7	25.8

Example 5

This example illustrates the use of a kit for in vivo parenteral screening of a lipophilic compound in a living organism model to evaluate pharmacokinetic profiles such as tolerability and bioavailability.

70 g of soybean lipid containing 90% phosphatidylcholine (PC) is dissolved under stirring and nitrogen in 20 g ethanol. 10 g of triclabendazole is dissolved under stirring in the ethanol phase containing the phospholipid. The resulting solution is then heated to 60°C and filtered under sterile conditions through a 0.45 µm pore size filter. 22 ml of the solu-

tion is filled into vials under nitrogen and closed with a rubber stopper and aluminium cap to ensure sterility. 20 ml of the contents of the vial is removed from the vial with a 20 ml syringe of Becton Dickinson, equipped with a 14 G needle and injected subcutaneously at a dose of 10 mg/kg into a cow of 200 kg.

Example 6

This example illustrates an example of a kit for examining biological properties such as oral bioavailability of a lipophilic test compound such as cyclosporine A.

10 mg of cyclosporine A is added to 2 kits each containing 20 mg lipid dissolved in 20 mg of ethanol or 50 mg of lipid dissolved in 50 mg of ethanol and left to dissolve for 1 hour at 50°C. The contents of the vials are emptied and diluted with 10 ml of distilled water. The amount of cyclosporin A associated with lipid is then determined by HPLC after filtration. The results of the association are provided in the table below:

Kit	2:1 lipid/drug ratio		5:1 lipid/drug ratio	
	Appearance	Association (%)	Appearance	Association (%)
28 % PC 62 % MAPC	Cloudy fine precipitate	67.3	Cloudy very fine precipitate	100.0
12 % PC 80 % MAPC	Clear liquid containing some fine precipitate	61.4	Clear liquid	100.0

The kits containing a lipid to drug ratio of 5:1 are administered orally to rats after dilution with distilled water.

Example 7

This example illustrates the use of a kit for applying a lipophilic compound to a living organism topically to screen for tolerability and bioavailability.

5 g of soybean lipid containing 45 - 50% phosphatidylcholine is dissolved under stirring and nitrogen in a mixture of 40 g isopropanol and 52 g of a citrate buffer (7.5 mM, with a pH 5.0). In addition, to give the formulation gel properties methylcellulose is dissolved up to 2 %. 1 g of hydrocortisone (Ph.Eur.) is dissolved under stirring in the liquid phase containing the phospholipid. The resulting gel is applied to a skin of a guinea pig to test for skin penetration of hydrocortisone.

In the examples illustrated above, in place of phospholipids other associate forming components such as cyclodextrin and urea may be substituted as appropriate.

Example 8

This example illustrates the suitability of a kit for screening a lipophilic compound with low water solubility intravenously to identify one or more desired physicochemical or biological property by using a Common component such as a cyclodextrin.

1350 mg of hydroxypropyl-beta-cyclodextrin (Wacker Chemie) is dissolved in 3.0 ml of water for injection, and aseptically filtered into a sterilised 5 ml container sealed with a rubber stopper and aluminium cap. The kit may comprise one or preferably a number of containers containing Common component(s) or, preferably the same component i.e. hydroxypropyl-beta-cyclodextrin.

600 µl of the cyclodextrin solution is withdrawn and added to 14.71 mg carbamazepine (Sigma) to form molecular associates. The resulting clear solution comprising solubilised carbamazepine is aseptically filtered before testing in animal models to obtain desired biological data such as tolerability and bioavailability, etc. Supporting physicochemical data and additional biological data may also be obtained using similar compositions with or without membrane lipids. In the event that the tests performed use a kit comprising the same Common component, the results may be collated and applied to a final formulation

more reliably. This is an example of a kit where the Common component comprises a cyclodextrin.

Example 9

An amount of an antiviral compound $C_{23}H_{21}N_5SF$ with low water solubility (0.00008 g/l), in the range between 2 mg to 20 mg is dissolved in 20 µl to 200 µl DMSO respectively, and held in test tubes.

5 ml of a kit composition comprising 12%w/w phospholipid suspension in aqueous medium is prepared by dispersing the lipid in 2.5% w/w glycerol at room temperature, followed by passage through an Avestin high pressure homogeniser. The mean particle size of the lipid particles as measured by photon correlation spectroscopy is ca. 40 nm. The suspension is sterile filtered through a 0.45 µm pores size filter and filled into a sterile glass vial using aseptic technique. The vials are sealed with a rubber stopper and aluminium cap.

20 µl to 200 µl of the antiviral compound solution is added under aseptic conditions in situ to the kit containing 5ml of lipid composition. The resulting test compositions are free from precipitated drug particles and may be injected directly into an animal for screening the biological properties of the antiviral compound.

It should be understood that one or a combination of the individual compositions without a test material shown in examples 1 to 9 above may be present in a kit.

Summary:

The present invention is concerned with a multipurpose, solubilising kit and methods thereof for obtaining in vitro as well as in vivo data. It describes a kit comprising preferably more than one container or such like comprising homogeneous solutions or dispersions of at least one Common component. The Common component has the potential and capacity to solubilise, or form complexes with new as well as existing compounds with low water solubility, for the assessment of physicochemical and/or biological properties in models. The physicochemical data may be e.g. solubility and membrane lipid interaction potential, whilst the biological data may include but not limited to information on

membrane permeability, bioavailability, efficacy, toxicity, pharmacokinetic (PK), distribution, elimination profiles, local tolerability, etc. The kit allows for an integrative approach, whereby the data from a series of tests can be collated and extrapolated more appropriately and reliably. The kit and methods thereof screens materials for pharmacokinetic and other biological properties for intravenous, intramuscular, subcutaneous, oral, topical or any other route of administration to a living organism.

Claims

1. A multipurpose kit for screening compounds with low water solubility and analysing for physicochemical and biological properties of said compounds which involves preparing one or more compositions comprising homogeneous solutions, dispersions or suspensions of, i) at least one Common component which has the potential and capacity to solubilise, or form molecular associates, ii) water or a water-miscible organic solvent, iii) mixtures thereof, and

   a) forming a solution, or molecular associates by mixing said compositions with a test material with low water solubility and, optionally after dilution with water, analysing the physicochemical properties, and/or

   b) forming a solution, or molecular associates by mixing with a test material with low water solubility and, optionally after dilution with an aqueous medium, adding said composition to cell models, cell lines or components of living organism and analysing the physicochemical properties, and/or

   c) forming a solution, or molecular associates by mixing with a test material with low water solubility and, optionally after dilution with an aqueous medium, administering said composition to living organisms and analysing the biological properties.

2. A kit according to claim 1 for obtaining physicochemical data on a test material comprising at least one membrane lipid, and a hydrophilic medium, said composition further comprising optionally other components and excipients, wherein said composition(s) is contained in one or more test tube, or sealed container or the like.

3. A kit according to claim 1 for obtaining biological properties of a test material comprising at least one cyclodextrin and a hydrophilic medium, said composition further comprising optionally other components and excipients, wherein said composition(s) is contained in one or more test tube, or sealed container or the like.

4. A kit according to claims 1-3 for obtaining biological properties of a test material comprising 0.1% to 90% by weight of at least one membrane lipid, or one cyclodextrin, or 0.1% to 0.9% by weight of a combination of membrane lipid and cyclodextrin, in solution or in dispersion in a hydrophilic medium, said composition further comprising optionally other components and excipients, wherein said composition(s) is contained in one or more test tube, or sealed container or the like.

5. A kit according to any one of claims 1 - 4 for obtaining physicochemical and biological data of test material comprising 0.1% to 70% by weight of at least one membrane lipid, or 0.1% to 70% by weight of a cyclodextrin, or 0.1% to 70% by weight of membrane lipid and cyclodextrin in any combination, in solution or dispersion in a hydrophilic medium, and optionally other components and excipients, wherein said composition(s) is contained in a test tube, or sealed container or the like.

6. A kit according to claim 1 for obtaining physicochemical and biological data of a test material comprising 0.1% to 20% by weight of one of the following: polysorbate 20, polysorbate 80, Cremophor EL®, Cremophor RH®, urea, in solution or dispersion in at least one hydrophilic medium, and optionally containing other components and excipients within a suitable container.

7. A kit according to claim 1 for obtaining physicochemical and biological data of test material comprising 0.1% to 20% by weight of a mixture of a bile salt and a lecithin in solution or dispersion in at least one hydrophilic medium, and optionally containing other components and excipients within a suitable container.

8. A kit for obtaining physicochemical and biological data of test material according to claims 1-7 comprising 0.1% to 99.9% by weight of water and/or one or more water miscible, organic solvent selected from the group consisting of ethanol, PEG 300, PEG 400, propylene glycol, glycerol, and ethyl lactate, and optionally containing other components and excipients within a suitable container.

9. A kit according to any of claims 1,3,4 and 5, wherein the cyclodextrin is selected from alpha, beta, gamma cyclodextrin, hydroxypropyl-beta and sulphobutylether-beta-cyclodextrin and other derivatives of cyclodextrin.

10. A kit according to any one of claims 1,2,4 and 5, wherein the lipid is selected from the group consisting of phospholipid, cardiolipin, sphingomyelin, cerebrosides, glycolipids, and ceramides.

11. A kit according to claim 10, wherein the lipid is diacyl phosphatidylcholine, or monoacyl phosphatidylcholine, or a mixture of diacyl and monoacyl components in a ratio of 1:20 to 20:1.

12. A kit according to claim 11, wherein the diacyl phosphatidylcholine is preferably selected from the group consisting of soy PC, Egg PC, POPC, and OOPC, and/or the monoacyl component is selected from the group consisting of enzyme modified (Phospholipase A2) soy PC, Egg PC, 1 -palmitoyl PC, 1 oleoyl PC, and 1-stearoyl PC.

13. A kit according to any one of claims 1 - 12 comprising at least one water miscible solvent which is selected from the group consisting of ethanol, 96% ethanol, absolute glycerol, propylene glycol, ethyl lactate, polyethylene glycol 300, polyethylene glycol 400, 1,3 butandiol, succinic acid diethyl ester, triethyl citrate, dibutyl sebacate, dimethyl acetamide, DMSO, glycerineformal, glycofurol (tetraglycol), isopropanol, lactic acid butyl ester, N-methylpyrrolidone, solketol, propylene carbonate, propylene glycol diacetate, tetrahydrofurfuryl alcohol, diethylene glycol mono ethyl ether, and triacetin.

14. A kit according to any one of claims 1 - 13 further comprising at least one pharmaceutically acceptable excipient which is selected from the group consisting of water for injection (e.g according to the United States Pharmacopoeia), benzyl alcohol, benzyl benzoate, triglycerides, medium chain triglycerides like Miglyol 810™, Miglyol 812™, Miglyol 812 N™, Miglyol 829™, Miglyol 840™ Miglyol 8810™, isopropyl myristate, isopropyl palmitate, ethyl oleate, (2-octyl dodecanol), laurinsäure hexyl ester, oleic acid, ricinus oil, sesame oil, soybean oil, anti-oxidants, and combinations thereof, said anti-oxidants being selected from the group consisting of alpha tocopherol acetate, ascorbyl palmitate and anit-microbial preservatives like methyl paraben and butyl paraben.

15. A kit according to any one of claims 1 - 14 for screening compounds with low water solubility to identify desired physicochemical and biological properties of said compounds.

16. A kit according to any one of claims 1 - 15, wherein said kit comprises one or more containers or sealed units for single use or multiple use, each container comprising one of at least one Common component, said Common component having the potential and capacity to dissolve or form molecular associates; water or a water-miscible organic solvent and mixtures thereof; and optionally containing further excipients.

17. A kit according to any one of claims 1 - 16 for mutually identifying test materials and components with desired physicochemical, or biological properties, or for both physiological and biological properties.

18. A kit according to claims 1,2,4,5 and 10-17 wherein said composition contains at least one diacyl membrane lipid or at least one monoacyl membrane lipid or a combination of monoacyl and diacyl membrane lipid and is suitable for oral or topical or parenteral administration to a living organisation.

19. A kit according to claims 1 - 18 wherein a total of at least 10 mg of a test material is used for the tests to obtain physicochemical and/or biological data.

20. A kit according to claims 1 - 19 prepared in situ.

21. A kit according to claims 1 - 20 for tests in situ.

22. A kit according to claims 1 - 21 for tests in vitro and/or in vivo .

23. A kit according to claims 1 - 22 comprising at least one solubilising composition in a suitable container which includes labelling and all associated packaging and instructions for screening compounds for data.